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Measurement of Relative Cerebral Blood Volume Changes with Visual Stimulation by 'Double-Dose' Gadopentetate-Dimeglumine-Enhanced Dynamic Magnetic Resonance Imaging

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KEY WORDS. Magnetic resonance imaging; dynamic; contrast agent; gadopentetate dimeglumine; cerebral blood volume; functional imaging; photic stimulation; calcarine cortex; lateral geniculus.

OVER THE LAST few years, there has been growing interest in using dynamic contrast-enhanced magnetic resonance imaging (DMRI)¹⁻⁶ for the assessment of cerebral function in response to somatosensory and cognitive stimulation. Using rapid-scanning MR techniques (ie, fast gradient-recalled echo or echo-planar pulse sequences) changes in relative regional cerebral blood volume (rCBV) can be detected in the primary visual cortex in response to visual stimulation.^{2,5,6} The determination of rCBV depends on changes in signal intensity on the MR image that corresponds to the first pass of a paramagnetic contrast agent through the parenchyma. Dynamic contrast-enhanced magnetic resonance imaging also been used to differentiate areas of ischemia from infarction in the central nervous sys-

tem.^{7,8} Other types of DMRI studies that depend on neural activation associated changes in the concentration of an endogenous paramagnetic compound, deoxyhemoglobin also may provide unique insight into cerebral function.⁹⁻¹⁶ However, other factors such as vascular inflow, blood volume, local hematocrit and oxygen use also may contribute to observed changes in the MRI signal with stimulation using this deoxyhemoglobin technique.

In this study, we attempted to determine the following: 1) if DMRI with a bolus injection of gadopentetate dimeglumine (Gd-DTPA) at 0.2 mmole/kg could be used to detect changes in rCBV in the lateral geniculate and calcarine cortex in response to photic stimulation; and to monitor for any side effects from a total dose of 0.4 mmole/kg of Gd-DTPA (four times the presently recommended clinical dose) given as two bolus injections.

Material and Methods

This study was approved by the Intramural Review Board of the National Institute of Mental Health at the National Institutes of Health. Fifty one healthy volunteers with no history of significant neurologic or ophthalmologic disease were enrolled in the study. Of those, 20 subjects studied with photic stimulation are reported on here. Magnetic resonance imaging scans were performed at 1.5 T on a GE Signa (General Electric, Milwaukee, WI) using the standard quadrature head coil and shielded gradients. Dynamic MRI studies were performed using a T2* sensitive echo-shifted (ES) fast low-angle shot (FLASH) pulse sequence with an effective echo time (TE) = 25 msec, a repetition time (TR) = 16 msec, flip angle (FA) of 20° (2.0 sec/image), a field of view of 24 cm, and a 128 × 256 matrix^{6,17}. Sixty sequential DMRI images were obtained before, during, and after an intravenous bolus injection (3 to 5 seconds) of Gd-DTPA (Magnevist, Berlex Labo-

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ratories, Wayne, NJ) at 0.2 mmole/kg followed by a 60-mL saline flush through an 18-gauge catheter placed in the antecubital vein. Photostimulation was started approximately 15 to 20 seconds before the injection of GdDTPA using a video projection system (Resonance Technology, Inc. Woodland Hills, CA) in which white light or an oscillating checkerboard pattern was projected onto a screen at a frequency of 7.8 Hz and viewed through the head coil mirror. Stimulated and unstimulated studies were performed in random order within 15 minutes of each other. Three-dimensional volume spoiled gradient-recalled acquisition in the steady state (SPGR) (TE = 5 msec, TR = 24 msec, FA = 45°) images were obtained before DMRI for anatomical localization. Vital signs were monitored, and a questionnaire was given to all subjects to observe for side effects from the two double-dose injections of Gd-DTPA.

Dynamic MR images were transferred to a Unix workstation and processed off-line using IDL (Research Systems, Inc. Boulder, CO). For each image, signal intensity (SI) versus time was converted to concentration (C) versus time using the following relationship:

$$C(t) = -\ln(S(t)/S_0) \quad (1)$$

in which $S(t)$ is the SI at each time t , S_0 is the baseline SI, and k is a proportionality constant correcting for TE, field strength and contrast agent used.^{2,5,6,18} Concentration versus time curves were then calculated for each pixel and were fitted using a gamma variate function.^{2,5,6,18,19} A pixel-by-pixel integration of the area under the fitted curves was used to create the relative CBV maps. Regions of interest (ROIs) were drawn on the anatomical SPGR images over the lateral geniculate nuclei (LG) and calcarine cortex (CC) and then were applied to the functional images to obtain the values of the rCBV in these regions. Statistical analysis was performed using a Student's t -test to compare the results from the stimulated and unstimulated studies.

Results

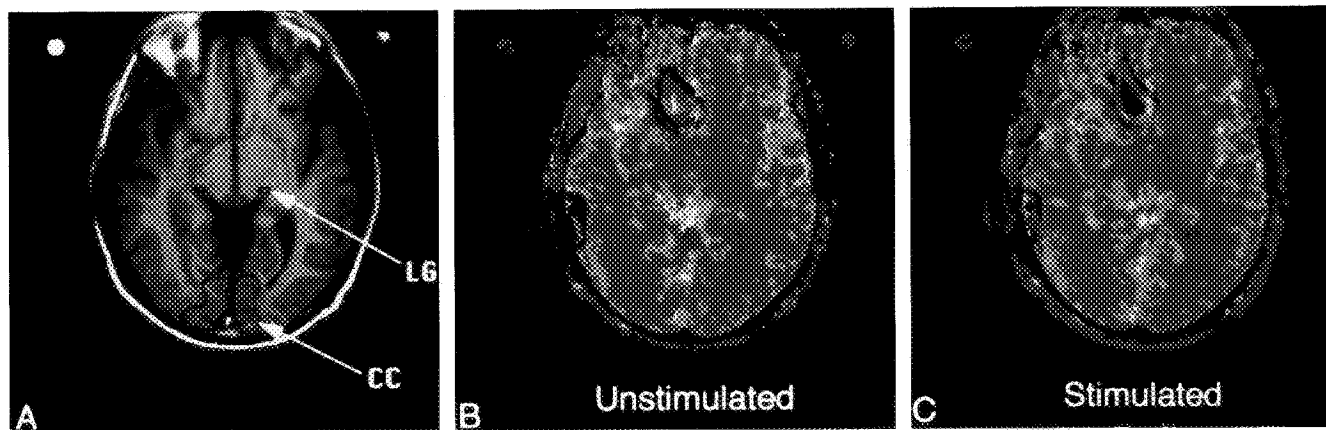
In all volunteers, changes in the SI caused by susceptibility effects associated with the first pass of Gd-DTPA through the cerebral vasculature of the CC were observed on the ES FLASH images. The ES FLASH pulse sequence provides a greater sensitivity to changes in $T2^*$ as Gd-

DTPA passes through the cerebral capillary network as compared to other gradient-recalled echo techniques.^{6,17} In five individuals, the DMRI study was positioned at a level that allowed for the detection of changes in SI in the LG and CC (Fig. 1). An example of the calculated rCBV maps for the unstimulated and visually stimulated conditions at the level of CC and LG are displayed in Figures 1B and 1C. When comparing the two conditions in this subject, there is an increase in signal on the rCBV map in the area of the calcarine cortex and lateral geniculate. A difference image was not created for the rCBV maps of the stimulated and unstimulated states because a single-pixel misregistration due to head motion between the two studies often resulted in artifacts. Instead, a plot of the concentration versus time curves from the ROIs in the CC and LG is presented in Figure 2. The percent differences between the area under curves for the stimulated and unstimulated conditions revealed a change in rCBV of $23.5 \pm 14.6\%$ (range 4%–50.4%) ($P < .009$) for the CC ($n = 20$) and $34.6 \pm 11.0\%$ (range 22.9–51.9) for the LG ($n = 5$).

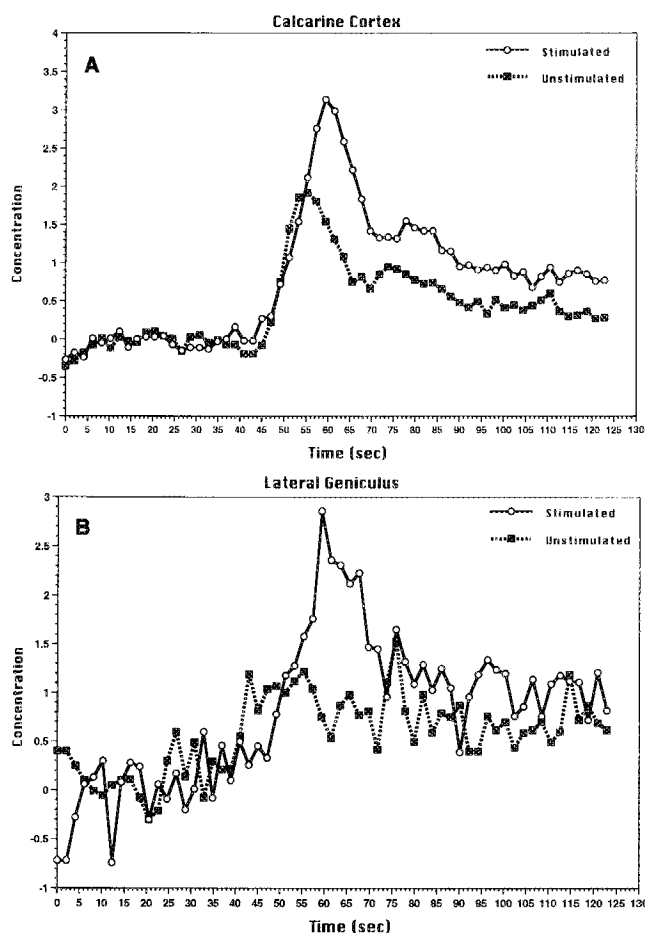
Table 1 is a list of the side effects for all of the 51 volunteers enrolled who received a total dose of 0.4 mmole/kg of Gd-DTPA administered as two bolus injections separated by 15 min (routine recommended dose of Gd-DTPA is 0.1 mmole/kg). All the subjects tolerated the two bolus injections of Gd-DTPA well, with minimal side effects. Only one subject had a 14 mm/Hg postural change in systolic blood pressure. Similar results have been found for a larger group of individuals with Gd-DTPA administered at 0.3 mmole/kg.²⁰

Discussion

The differences in the rCBV in the visual cortex between stimulated and unstimulated studies are consistent with the results reported by other researchers using other types of



Figs. 1A–1C. Representative spoiled gradient-recalled acquisition in the steady state (SPGR) image from a three-dimensional volume data acquisition set at the level of the calcarine cortex including area of lateral geniculate nuclei (A). Regions of interest for the calcarine cortex and lateral geniculate nuclei are drawn on the magnetic resonance image to delineate area from which concentration versus time curves were obtained for Figure 2. (B, C) Fitted relative cerebral blood volume maps for the unstimulated and photostimulated conditions. The apparent difference between the two conditions is readily appreciated.



Figs. 2A and 2B. Plot of the concentration versus time curves for the regions of interest shown in Figure 1A for the calcarine cortex (A) and for the lateral geniculate nuclei (B). By fitting the area under the curve with a gamma variate function on a pixel-by-pixel basis, relative cerebral blood volume maps can be obtained as shown in Figures 1B and 1C.

fast MRI pulse sequences and hardware, and/or varying Gd-DTPA dose.^{2,5,6} To our knowledge, however, this is the first report of changes in rCBV in the lateral geniculate in response to visual stimulation in man. The LG is 6 to 10 mm and is the main thalamic nucleus conveying information from the retina to the primary visual cortex. Quantitative physiological studies of the LG have only been performed in animals using electrophysiological recording or autoradiographic techniques.²¹ Based on the preliminary re-

sults found using five subjects, it appears that the percentage change in rCBV with visual stimulation in the LG is similar to that observed for the CC. Further study is required to see if the results can be reproduced in a larger group of subjects using different stimuli to examine the retinotopic mapping in the LG.

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) have some advantages over DMRI in the evaluation of cerebral function.²² Dynamic MRI examinations are currently performed in a single slice only, and therefore, small "activated" structures in the central nervous system could easily be missed because they are located outside the volume of interest. Although PET and SPECT are multislice techniques, they have limited spatial and temporal resolution compared with DMRI. Dynamic MRI studies cannot at this time be quantitated in classical units of blood flow (ie, mL/100 grams of tissue/min), a measurement that is possible with PET. Difficulties in obtaining the arterial input function limits the ability to perform absolute quantitation with DMRI and allow for the determination of the mean transit times (MTT), the cerebral blood flow (CBF) and CBV in response to stimulation paradigms. To obtain an arterial input function, it would be necessary to monitor an artery on an adjacent slice, thus requiring multislice capabilities. Another limitation of DMRI technique is the optimum coordination of the bolus injection of the contrast agent to the task to maximize the changes in the rCBV. Steady state based approaches such as PET, SPECT, and MRI studies with arterial tagging²³ or using changes in deoxyhemoglobin within brain capillaries and venules may be better suited for studying changes in brain physiology with complex tasks.^{9-16,18,22} Multislice or three-dimensional volume techniques that have recently been developed should provide the increased flexibility needed to improve on the limitations of DMRI.^{24,25}

The advantages of functional MRI over nuclear medicine techniques include the following: 1) the lack of ionizing radiation; 2) the need for a cyclotron as for PET; and 3) the ability to repeat multiple studies as often as desired during the calendar year. In our experience, the functional information obtained from DMRI examinations also may be improved by the following: 1) shimming over the volume of interest thereby improving the main magnetic field (B_0) homogeneity; 2) the use of specialized gradient coil systems;¹² 3) using a mechanical injector to obtain reproducible bolus injections of the contrast agent; 4) the introduction of a paramagnetic or superparamagnetic contrast agent that causes a greater change in $T2^*$ per unit volume;^{3,26} and 5) the development of more robust algorithms for data analysis and quantitation.^{6,27,28} Positron emission tomography, SPECT and functional MRI should be considered complementary in providing a better understanding of normal cerebral function and pathophysiology of central nervous system disorders.

TABLE 1. Somatic Side Effects with Two Bolus Injections of Gadolinium-DTPA 0.2 mmole/kg (51 volunteers)

Headache	1/51
Nausea	3/51
Warmth in arm	23/51
Warmth in arm	13/51
Local discomfort at intravenous site	1/51
Taste or smell	15/51
Oropharyngeal sensation	13/51

Conclusions

This study using dynamic ES FLASH imaging in conjunction with a bolus injection of Gd-DTPA at 0.2 mmole/kg demonstrated in normal volunteers significant differences in the relative cerebral blood volume in the calcarine cortex and lateral geniculus between photic stimulated and unstimulated studies. In addition, subjects tolerated two bolus injections of double-dose Gd-DTPA with minimal side effects suggesting that future multitask studies requiring a larger cumulative dose of Gd-DTPA should be well tolerated.

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References

1. Moonen CTW, van Zijl P, Frank JA, Le Bihan D, Becker ED. Functional magnetic resonance imaging in medicine and physiology. *Science* 1990;250:53-61.
2. Belliveau JW, Kennedy DN, McKinstry RC, et al. Functional mapping of the human visual cortex by magnetic resonance imaging. *Science* 1991;254:716-719.
3. Zigun JR, Frank JA, Barrios FA, et al. Measurement of brain activity with bolus administration of contrast agent and gradient echo MR imaging. *Radiology* 1993;186:353-356.
4. Frank JA, Doudet D, Saunders R. Dynamic dysprosium-DTPA-BMA enhanced MRI of the occipital cortex: functional imaging in visually impaired monkeys by PET and MRI. *Society of Magnetic Resonance in Medicine* 1990;1:188.
5. Alger JR, Frank JA. The utilization of magnetic resonance imaging in physiology. *Ann Rev Physiol* 1992;54:827-846.
6. Moonen TW, Zigun JR, Gillen J, et al. Functional MR imaging with novel T₂*-sensitized gradient echo methods: demonstration of human visual cortex activation using bolus tracking. *Magn Reson Imaging* 1994. In press.
7. Edelman RR, Mattle HP, Atkinson DJ, et al. Cerebral blood flow: assessment with dynamic contrast enhanced T₂*-weighted MR imaging at 1.5 Tesla. *Radiology* 1990;176:211-220.
8. Tzika AA, Massoth RJ, Ball WS, Majumdar S, Dunn RS, Kirks DR. Cerebral perfusion in children: detection with dynamic contrast-enhanced T₂* weighted MR images. *Radiology* 1993;187:449-458.
9. Ogawa S, Tank DW, Menon R, et al. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proc Natl Acad Sci* 1992;89:5951-5955.
10. Kwong KK, Belliveau JW, Chesler DA, et al. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc Natl Acad Sci* 1992;89:5675-5679.
11. Frahm J, Bruhn H, Merboldt KD, Hanicke W. Dynamic MR imaging of human brain oxygenation during rest and photic stimulation. *Magn Reson Med* 1992;2:501-505.
12. Bandettini PA, Wong EC, Hinks RS, Tikofsky RS, Hyde JS. Time course EPI of human brain functions during task activation. *Magnetic Reson Med* 1992;25:390-397.
13. Shulman RG, Blamire AM, Rothman DL, McCarthy G. Nuclear magnetic resonance imaging and spectroscopy of human brain function. *Proc Natl Acad Sci* 1993;90:3127-3133.
14. Turner R, Jezzard P, Wen H, Kwong KK, Le Bihan D, Zeffiro T, Balaban RS. Functional Mapping of the human visual cortex at 4 and 15 Tesla using deoxygenation contrast EPI. *Magn Reson Med* 1993;29:277-279.
15. Kim SG, Ashe J, Hendrich K, et al. Functional magnetic resonance imaging of motor cortex: hemispheric asymmetry and handedness. *Science* 1993;261:615-617.
16. Connelly S, Jackson GD, Frackowiak RSJ, Belliveau JW, Vargha-Khadem F, Gadian DG. Functional mapping of activated human primary cortex with a clinical MR imaging system. *Radiology* 1993;188:125-130.
17. Liu G, Sobering G, Olson AW, van Gelderen P, Moonen CTW. Fast echo-shifted gradient-recalled MRI: Combining a short repetition time with variable T₂* weighting. *Magn Reson Med* 1993;30:68-75.
18. Rosen B, Belliveau JW, Chien D. Perfusion Imaging by Nuclear Magnetic Resonance. *Magn Reson Q* 1989;5:263-281.
19. Thompson HK, Starmer CF, Whalen RE, McIntosh HD. Indicator transit time considered as a gamma variate. *Circ Res* 1964;14:502-514.
20. Neindorf HP, Hausteijn J, Louton T, Beck W, Laniado M. Safety and tolerance after intravenous administration of 0.3 mmole/kg Gd-DTPA: results of a randomized control clinical trial. *Invest Radiol* 1991;26(suppl):S221-S223.
21. Casagrande VA, Norton TT. Lateral geniculate nucleus: a review of physiology and function. In: Leventhal AG, ed., *Vision and visual dysfunction. Volume 4: the neural basis of visual function*. Boston: CRC Press; 1991:41-85.
22. Fox PT, Raichle ME. Stimulus rated dependence of regional cerebral blood flow in human striate cortex, demonstrated by positron emission tomography. *J Neurophysiol* 1984;51:1109-1120.
23. Detre JA, Leigh JS, Williams DS, Koretsky AP. Perfusion imaging. *Magn Reson Imaging* 1992;23:37-45.
24. Duyn JH, Moonen CTW, Mattay VS, et al. 3 dimensional functional imaging of human brain using echo-shifted flash. *Society of Magnetic Resonance in Medicine* 1993;3:1386.
25. Liu G, Sobering G, Duyn J, Moonen CTW. A functional MRI technique combining principles echo-shifting with a train of observations (PRESTO). *Magn Reson Med* 1993;30:764-768.
26. Moseley ME, Vexler Z, Asgari HS, et al. Comparison of Gd-and Dy-chelates for T₂* contrast enhanced imaging. *Magn Reson Med* 1991;22:259-264.
27. Bandettini PA, Jesmanowicz A, Wong EC, Hyde JS. Processing strategies for time-course sets in functional MRI of the human brain. *Magn Reson Med* 1993;30:161-173.
28. Rogowska J, Wolf GL, Rogowska J, Wolf GL. Temporal correlation images derived from sequential MR scans. *J Comput Assist Tomogr* 1992;16:784-788.